PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 12367500/TDO/FT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/AU2003/001497	International Filing Date *(day/month/year)* 13 November 2003	Priority Date *(day/month/year)* 13 November 2002

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] C12N 5/00, 5/06, 5/08

Applicant

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1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
31 May 2004	21 February 2005
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **TERRY MOORE** Telephone No. (02) 6283 2632

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001497

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of: —

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**13, 14 and 26-29**	**YES**
	Claims	**1-12, 15-25, 30 and 31**	**NO**
Inventive step (IS)	Claims	**13, 14, 28 and 29**	**YES**
	Claims	**1-12, 15-27, 30 and 31**	**NO**
Industrial applicability (IA)	Claims	**1-31**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

The invention relates to methods of detecting clonal populations of cells by co-localising a subject nucleic acid region from a population of cells in a biological sample and assessing the level of the co-localised nucleic acid relative to a background level, where a higher comparative level is indicative of a clonal population of cells. In particular the description exemplifies assessing the mitochondrial D-loop region using denaturing gradient gel electrophoresis (DGGE).
The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 Cancer Research 61, 7015-19
D2 Biochem Biophys Res Comm 199, 511-18
D3 Diagnost Mol Path 6, 140-6
D4 Diagnost Mol Path 6, 71-77
D5 J Surg Res 85, 311-16
D6 Leukemia 8, 946-52
D7 J Neuropath Exp Neurol 61, 396-402
D8 J Clin Path: Mol Path 53, 150-54
D9 Int J Parasitol 32, 27-38
D10 WO 2002 088388
D12 US 2002/0004201

Novelty and Inventive Step

Documents D1 and D10 are not directly relevant to the novelty or inventive step of the claims. Although D1 discloses mutations in the D loop in cancers and use of this region to identify the origin and clonality of cancer cells, it does not disclose co-localising nucleic acid regions. It simply discloses amplification and sequencing. D10 discloses a method of characterising mutation loads and heterozygosity, but does not suggest that such a method can also be used to characterise the extent of clonality.

D2 discloses a method of detecting and assessing clonality using PCR to amplify target regions and DGGE to identify, quantify and compare levels of different variants within a population of cells. The target regions are an intron in the HPRT gene and a region in the PGK gene and the clonality is associated with cancer. As such D2 deprives claims 1-3, 11, 15-18, 26, 30 and 31 of novelty and an inventive step.

Continued in supplemental box.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-14 and 17-29 are not fully supported by the description. The description discloses methods of co-localisation that separate and co-localise variants on the basis of differing molecular sizes of the variants arising from nucleic acid sequence variations within a distinctive nucleic acid region. The relative amounts of the separated variants are then used to generate a profile that is compared with a background profile of the region.

In contrast the claims do not specify that the method requires separation on the basis of sequence variation and molecular size followed by preparation of a profile that reflects relative amounts of sequence variants. As such the claims do not recite all of the essential features that define the applicant's invention.

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V2

D3-D6 disclose the use of PCR and denaturing PAGE to characterise clonality in B and T cell cancers, in particular lymphomas and leukaemias. As such D3-D6 deprive claims 1-5, 8, 9, 11, 15-20, 23, 24, 26, 30 and 31 of novelty and an inventive step.

D8 also discloses the use of PCR and PAGE to characterise clonality in T cell populations. However D8 is not restricted to T cell cancers and discusses other T cell conditions. As such, D8 is not only relevant to the novelty and inventive step of claims 1-5, 8, 9, 11, 15-20, 23, 24, 26, 30 and 31, it also deprives claims 6 and 21 of novelty and an inventive step.

D7 discloses the use of PCR and electrophoresis to identify clonality in gliomas. In particular the citation assesses differences in microsatellite sequences. As such D7 deprives claims 1-3, 11, 12, 15-18, 26, 27, 30 and 31 of novelty and an inventive step.

In addition, D7 also deprives claims 4, 5 and 19 of an inventive step. Although these claims relate to methods of assessing clonality in B and T cell cancers and D7 relates to gliomas, the discussion in D7 discloses the use of such a technique for assessing clonality in a range of neoplasms. Given this disclosure, it would be obvious to apply the method disclosed in D7 to other standard neoplasms, such as those associated with immune cell cancers.

D9 discloses analysis of clonality in populations of the single-celled parasiste *Toxoplasma gondii* using PCR and electrophoresis. The regions that is analysed is a microsatellite region. As such D9 deprives claims 1, 2, 6, 10-12, 15-17, 21, 25-27, 30 and 31 of novelty and an inventive step.

D11 discloses analysis of loss of heterozygositiy and assessment of clonality in a range of cells and populations, including populations comprising cancerous cells and populations of microorganisms. The anaylsis includes PCR amplification and binding of probes to specific variants. The selected populations of variants may then be separated or co-localised as a consequence of affinity binding of the probes to binding matrices or as a consequence of separation of probes based on differing molecular weight or size. As such D11 deprives claims 1-11, 15-25, 30 and 31 of novelty and an inventive step.